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Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

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Abstract

Background: The benefit of cytoreductive nephrectomy (CN) for overall survival (OS) is unclear in patients with synchronous metastatic renal cell carcinoma (mRCC) in the era of targeted therapy.
Objective: To determine OS benefit of CN compared with no CN in mRCC patients treated with targeted therapies.
Design, setting, and participants: Retrospective data from patients with synchronous mRCC ($n = 1658$) from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) were used to compare 982 mRCC patients who had a CN with 676 mRCC patients who did not.
Outcome measurements and statistical analysis: OS was compared and hazard ratios (HRs) adjusted for IMDC poor prognostic criteria.
Results and limitations: Patients who had CN had better IMDC prognostic profiles versus those without (favorable, intermediate, or poor in 9%, 63%, and 28% vs 1%, 45%, and 54%, respectively). The median OS of patients with CN versus without CN was 20.6 versus 9.5 mo ($p < 0.0001$). When adjusted for IMDC criteria to correct for imbalances, the HR of death was 0.60 (95% confidence interval, 0.52–0.69; $p < 0.0001$). Patients estimated to survive <12 mo may receive marginal benefit from CN. Patients who have four or more of the IMDC prognostic criteria did not benefit from CN. Data were collected retrospectively.

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Conclusions: CN is beneficial in synchronous mRCC patients treated with targeted therapy, even after adjusting for prognostic factors. Patients with estimated survival times <12 mo or four or more IMDC prognostic factors may not benefit from CN. This information may aid in patient selection as we await results from randomized controlled trials.
Patient summary: We looked at the survival outcomes of metastatic renal cell carcinoma patients who did or did not have the primary tumor removed. We found that most patients benefited from tumor removal, except for those with four or more IMDC risk factors.

1. Introduction

Over the past decade, our molecular understanding of metastatic renal cell carcinoma (mRCC) has vastly improved. Since 2005, targeted therapies have been designed to target pathways involved in RCC pathogenesis, leading to the approval of the vascular endothelial growth factor (VEGF) inhibitors sunitinib, sorafenib, pazopanib, bevacizumab, and axitinib, and the mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus. Targeted therapies have demonstrated impressive gains in overall survival (OS), progression-free survival (PFS), and response rates over the previously utilized immunotherapies [1–3].

In the era of immunotherapy (1992–2004), a combined analysis of two prospective randomized clinical trials from the European Organization for Research and Treatment of Cancer (EORTC) and SWOG demonstrated that cytoreductive nephrectomy (CN) followed by interferon-α treatment had a 5.8-mo increased OS versus immunotherapy alone (13.6 vs 7.8 mo) [4–6]. The results solidified the role of CN in the immunotherapy era of mRCC treatment. However, with more effective targeted therapies largely supplanting immunotherapy, it is not well understood if CN should remain a part of the standard treatment protocol. The rates of CN have declined since the introduction of targeted therapy [7,8]. This large retrospective international study was performed to address the survival benefit of CN in mRCC patients treated with targeted therapy.

2. Methods

2.1. Patient population

Patient data were collected from 20 international cancer centers from Canada, the United States, Belgium, South Korea, Japan, Denmark, Greece, and Singapore. Patient inclusion criteria were composed of mRCC diagnosis of any type and treatment with a VEGF or mTOR targeted therapy (sunitinib, sorafenib, axitinib, bevacizumab, temsirolimus, pazopanib, or everolimus).

Data were collected using uniform database software and templates. Demographic, clinical, and laboratory data include those found to have prognostic value [9–11] (Table 1). Laboratory values were standardized against their respective institution upper limit of normal (ULN) and lower limit of normal (LLN) values as necessary. Measured outcomes included OS and PFS. This study received institutional review board approval from each participating center.

2.2. Statistical analysis

The primary outcome was OS from the initiation of first-line targeted therapy to the date of death or censored at last follow-up. PFS was defined as the initiation of targeted therapy to the date of progression, drug cessation, or censored at last follow-up. Median OS and PFS distributions were estimated using the Kaplan-Meier method.

Cox proportional hazards regression was used to determine hazard ratios (HRs) for OS after adjustment for known International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic factors: hemoglobin below LLN, corrected calcium greater than ULN, neutrophils above ULN, platelets greater than ULN, Karnofsky performance status <80%, and time from diagnosis to treatment <1 yr [11]. Adjusted HRs and p values were reported. Subgroup analysis and HRs were determined for IMDC favorable-, intermediate-, and poor-risk groups as well as other covariates of interest.

Incremental survival benefits were compared between those who received a CN versus those who did not in patients who survived <3, 6, 9, 12, 18, and 24 mo. An exploratory subgroup analysis of patients with 0–6 of the IMDC prognostic factors was performed to determine any differences in OS. Statistical analyses were performed with SAS v.9.2, defining $p < 0.05$ (two sided) as statistically significant.

3. Results

3.1. Patient characteristics and outcomes

A total of 2569 of 3245 IMDC mRCC patients (79%) received a nephrectomy. Patients who had a nephrectomy before the diagnosis of metastatic disease (ie, those with metachronous metastases) were excluded (n = 1587). Among remaining patients (n = 1658), 982 underwent a CN; 676 did not. These were the final numbers for analysis. The median follow-up of all patients was 39.1 mo (95% confidence interval [CI], 36.0–41.5). At the time of analysis, 1137 patients (68.6%) had died, and 1416 (85.4%) had experienced disease progression.

All patients received targeted therapy, with most receiving first-line sunitinib (72%). Table 1 shows the comparison of baseline characteristics between CN and non-CN patients. Patients receiving a CN had better IMDC prognostic profiles: 9% favorable, 63% intermediate, and 28% poor compared with the non-CN profiles, 1% favorable, 45% intermediate, and 54% poor ($p < 0.001$). Fewer CN patients had non–clear cell pathology ($p = 0.042$), bone metastases ($p = 0.001$), and liver metastases ($p = 0.001$), but CN patients had more sarcomatoid features (<0.001).

3.2. Univariable and multivariable analysis

The median OS for CN patients was 20.6 versus 9.6 mo for patients not receiving a CN (Fig. 1; $p < 0.001$). After adjustment with IMDC risk factors that were different between the two populations, a clear OS benefit was

Table 1 – Patient characteristics at initiation of targeted therapy by nephrectomy status

Baseline characteristics	No CN (n = 676), n/n (%)	CN (n = 982), n/n (%)	p value
Age, yr*	59.9 (54.6–70.0)	59.3 (52.7–67.4)	0.740
Gender			
Male	488/676 (72)	721/982 (73)	0.579
Female	188/676 (28)	261/982 (27)	
IMDC prognostic criteria			
Favorable	5/482 (1)	65/686 (9)	<0.001
Intermediate	215/482 (45)	431/686 (63)	
Poor	261/482 (54)	190/686 (28)	
KPS <80	233/558 (42)	158/837 (19)	<0.001
Diagnosis to targeted therapy <1 yr	639/674 (95)	695/980 (71)	<0.001
Serum corrected calcium >ULN	120/601 (20)	76/867 (8.8)	<0.001
Hemoglobin <LLN	446/643 (69)	570/907 (63)	<0.008
Neutrophils >ULN	166/624 (27)	127/881 (14)	<0.001
Platelets >ULN	167/595 (28)	164/803 (20)	0.001
Type of targeted therapy			
Sunitinib	533/675 (79)	654/972 (67)	<0.001
Sorafenib	58/675 (8.6)	194/972 (20)	
Axitinib	3/675 (0.4)	4/972 (0.4)	
Bevacizumab	10/675 (1.5)	42/972 (4.0)	
Temsirolimus	43/675 (6.4)	35/972 (3.6)	
Pazopanib	19/675 (2.8)	27/972 (2.8)	
Everolimus	9/675 (1.0)	9/972 (1.0)	
Other	2/675 (0.3)	7/972 (0.7)	
Non–clear cell pathology	83/533 (16)	113/954 (12)	0.042
Sarcomatoid features	38/442 (8.6)	151/936 (16)	<0.001
Bone metastases	305/638 (48)	359/908 (40)	0.001
Liver metastases	153/614 (25)	151/844 (18)	0.001
Brain metastases	64/608 (11)	72/903 (8)	0.089

CN = cytoreductive nephrectomy; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; KPS = Karnofsky performance score; LLN = lower limit of normal; ULN = upper limit of normal.
* Data are shown as median (interquartile range).

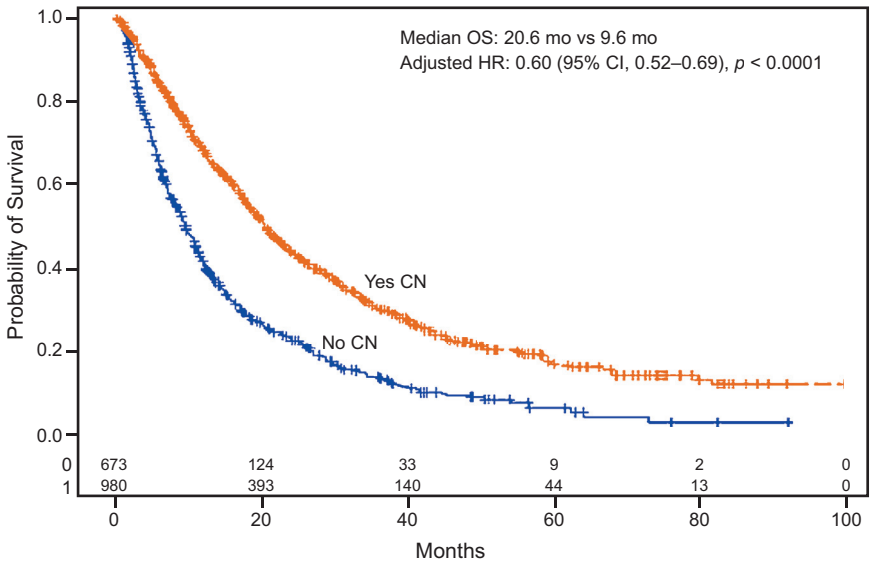

Fig. 1 – Kaplan-Meier curve depicting the overall survival from the initiation of targeted therapy for 1633 metastatic renal cell carcinoma patients who did or did not receive a cytoreductive nephrectomy.
CI = confidence interval; CN = cytoreductive nephrectomy; HR = hazard ratio; OS = overall survival.

observed in CN patients (HR: 0.60; 95% CI, 0.52–0.69; $p < 0.001$). CN was also associated with an increase in PFS: 7.6 mo (95% CI, 6.7–8.1; $p < 0.001$) versus 4.5 mo (95% CI, 3.9–5.1; $p < 0.001$). PFS adjustment for prognostic factors continued to show a benefit for CN (HR: 0.75; 95% CI, 0.66–0.85; $p < 0.001$). Table 2 shows the subgroup analysis of patients receiving CN compared with those not receiving CN.

Table 2 – Subgroup analysis of patients receiving and not receiving cytoreductive nephrectomy

Subgroup analysis	Median OS, mo		Hazard ratio (95% CI)	*p* value
	Without CN	With CN		
Risk				
Favorable*	41.0	37.0	–	–
Intermediate	13.3	23.0	0.58 (0.47–0.71)	<0.001
Poor	6.0	9.5	0.64 (0.52–0.78)	<0.001
KPS				
>80	12.2	23.4	0.53 (0.45–0.62)	<0.001
<80	5.3	8.6	0.70 (0.56–0.88)	0.002
Age at TKI, yr				
<75	9.6	20.8	0.52 (0.46–0.59)	<0.001
>75	8.6	16.7	0.66 (0.44–0.98)	0.038
No. of metastases				
1	15.0	38.6	0.50 (0.38–0.66)	<0.001
>1	8.9	17.7	0.55 (0.48–0.63)	<0.001
Brain metastases				
No	9.5	21.9	0.51 (0.45–0.58)	<0.001
Yes	6.9	12.5	0.57 (0.39–0.83)	0.003
Liver metastases				
No	10.7	21.5	0.53 (0.46–0.61)	<0.001
Yes	6.6	10.6	0.65 (0.51–0.84)	0.001
Bone metastases				
No	9.5	24.3	0.48 (0.40–0.56)	<0.001
Yes	9.3	14.9	0.65 (0.54–0.77)	<0.001
Sarcomatoid				
No	10.9	22.3	0.51 (0.44–0.59)	<0.001
Yes	5.5	10.2	0.56 (0.36–0.86)	0.009
Non–clear cell				
No	10.9	21.4	0.52 (0.45–0.59)	<0.001
Yes	8.0	15.3	0.61 (0.43–0.87)	0.006

CI = confidence interval; CN = cytoreductive nephrectomy; KPS = Karnofsky Performance Score; OS = overall survival; TKI = tyrosine kinase inhibitor.
* Numbers too small.

Table 3 – Incremental overall survival benefit from cytoreductive nephrectomy separated by estimated survival times

OS, mo	No CN OS, mo	CN OS, mo	Incremental benefit, mo	*p* value	HR (95% CI) adjusted for IMDC criteria
<24	7.1 *n* = 456	12.3 *n* = 480	+5.2	<0.0001	0.72 (0.62–0.85) *p* < 0.001 *n* = 676*
<18	6.7 *n* = 430	10.0 *n* = 395	+3.3	<0.0001	0.85 (0.72–1.00) *p* = 0.05 *n* = 602*
<12	5.5 *n* = 366	7.3 *n* = 290	+2.2	<0.0001	0.97 (0.81–1.17) *p* = 0.761 *n* = 483*
<9	4.5 *n* = 303	5.5 *n* = 218	+1.0	0.0027	0.98 (0.79–1.20) *p* = 0.811 *n* = 385*
<6	3.2 *n* = 230	4.0 *n* = 151	+0.8	0.0084	1.02 (0.80–1.31) *p* = 0.856 *n* = 280*
<3	2.1 *n* = 118	2.2 *n* = 71	+0.1	0.9429	1.03 (0.72–1.46) *p* = 0.878 *n* = 146*

CI = confidence interval; CN = cytoreductive nephrectomy; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival.
* The *n* used in the adjusted HR does not match the sum of CN versus no CN patients in each row due to missing data on prognostic factors because a complete case analysis was used.

3.3. *Incremental benefit analysis*

Incremental benefit analysis (Table 3) demonstrated that the only patient group not to receive an OS benefit from CN were those estimated to survive <3 mo (2.2 vs 2.1 mo OS: +0.1; $p = 0.943$). Patients estimated to survive ≤6 mo experienced a marginal +0.8 OS increase when a CN was performed (4.0 vs 3.2 mo OS; $p = 0.008$). The longer a patient was estimated to survive, the greater the OS benefit of CN. Patients estimated to survive <24 mo had an OS benefit of

Table 4 – Overall survival differences in those with and without cytoreductive nephrectomy by number of International Metastatic Renal Cell Carcinoma Database Consortium criteria met

No. of IMDC criteria met	No CN OS, mo (*n*)	CN OS, mo (*n*)	*p* value
0	92% of patients (65/71) had CN, insufficient number to compare		
1	22.5 (*n* = 72)	30.4 (*n* = 178)	0.002
2	10.2 (*n* = 143)	20.2 (*n* = 253)	<0.001
3	10.0 (*n* = 113)	15.9 (*n* = 106)	<0.001
4	5.4 (*n* = 103)	6.0 (*n* = 67)	0.166
5	3.6 (*n* = 36)	2.8 (*n* = 14)	0.504
6	25% of patients (3/12) had CN, insufficient number to compare		

Overall, 1168 of 1658 subjects (70%) had complete information about prognostic factors, nephrectomy, and outcomes and were used in this complete case analysis; the rest were excluded. Shaded rows indicate patient groups that may not benefit from cytoreductive nephrectomy.
CN = cytoreductive nephrectomy; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival.

+5.2 mo (12.3 vs 7.1 mo OS; $p < 0.001$). However, upon adjusting for prognostic factors, HRs were not significant for those who lived <3, 6, and 12 mo. Patients who lived <18 mo (HR: 0.85; 95% CI, 0.72–1.00; $p = 0.05$) and <24 mo (HR: 0.72; 95% CI, 0.62–0.85; $p < 0.001$) were more likely to derive benefit.

3.4. *International Metastatic Renal Cell Carcinoma Database Consortium criteria for patient selection*

Patients with no prognostic factors were not analyzed because almost all patients (92% [65 of 71]) had CN. At the other end of the spectrum, those with all six risk factors represented only 12 patients of whom only 3 (25%) received a CN. Those with one, two, and three risk factors seemed to derive benefit from CN, whereas those with four, five, and six risk factors did not (Table 4). A test for interaction between the number of IMDC prognostic factors and nephrectomy status was statistically significant ($p = 0.0005$), indicating that the prognostic factors modify the effect of nephrectomy on survival.

4. Discussion

The need for CN in the treatment of mRCC during the era of targeted therapy has been questioned due to the lack of supporting level 1 evidence. VEGF and mTOR inhibitors have demonstrated substantial improvements in tumor shrinkage and survival over previously used immunotherapies; thus there is concern over delaying treatment to perform a CN [2,12–14].

Although nephrectomies are a fairly safe procedure, CNs carry a higher mortality rate, and they are associated with higher morbidity and in-hospital complications that may reduce quality of life during recovery compared with those without CN [15]. However, CN is used as an inclusion criterion for some clinical trials or at least included patients with a vast majority having CN; thus determining if CN is indeed beneficial will have broad implications as to how mRCC treatment and research is managed.

To date, this study is the largest analysis demonstrating that CN provides an OS benefit in patients treated with targeted therapy while also adjusting for known prognostic factors. Our findings suggest that a large benefit exists in both OS and PFS in patients receiving a CN compared with those without, even after adjusting for imbalances in prognostic criteria (HR: 0.60; 95% CI, 0.52–0.69; $p < 0.001$ and HR: 0.75; 95% CI, 0.66–0.85; $p < 0.001$, respectively). The results are consistent with our previous analysis of a smaller cohort of 314 patients from the IMDC that demonstrated a median OS of 19.8 versus 9.4 mo ($p < 0.01$) and an adjusted HR of 0.68 (95% CI, 0.46–0.99; $p = 0.04$); however, there were no analyses to elucidate patient selection criteria [16]. The HR is similar to the EORTC trial performed in the age of immunotherapy (HR: 0.54; 95% CI, 0.31–0.94) [5].

A large study examining CN and survival in both the era of immunotherapy and targeted therapy noted an OS of 19 mo for targeted therapy with CN versus only 4 mo for targeted therapy alone [7]. Because this was performed with Surveillance Epidemiology and End Results (SEER) data, prognostic factors were unavailable and therefore not adjusted for. The results also showed a steady decrease in CN utilization, which peaked at 39% in 2004 and has decreased by 0.6% every year since then [7]. The declining trend of CN after the introduction of targeted therapy was observed elsewhere [8]. However, both of these studies used SEER data that focuses exclusively on the United States; thus it is difficult to ascertain if this is a global trend.

Careful patient selection is critical in determining if a patient will benefit from a CN because those with poor survival outcome or who are likely to progress rapidly may receive minimal benefit. In our incremental benefit analysis, CN provided an increase in OS for patients surviving <6 mo; however, when adjusted for prognostic factors, a significant HR was not observed until the <18-mo group. Thus patients expected to survive <12 mo may receive marginal benefit from a CN. Patients with four, five, and six IMDC risk factors did not appear to derive benefit.

Strengths of our analysis include the large multicenter series of patients that focuses on patients treated with targeted therapies [17]. Unlike clinical trials, the IMDC does not have inclusion criteria, strengthening its use as a population-based method of analysis. To our knowledge, this study is novel in examining the incremental benefits of CN and using the IMDC prognostic model factors to aid in patient selection.

Limitations of our study included that it was retrospective and patients may be prone to selection bias, although the use of consecutive patient series from registry and pharmacy data attempted to mitigate that. Our study is also limited in our ability to adjust for prognostic factors that are unknown or not collected because it is not possible to control for all factors, and we were unable to account for perioperative mortality or surgery-related morbidity. Missing data were handled using a complete case analysis; thus any patient with a missing prognostic factor would be excluded from the adjusted analyses to provide the most conservative estimate. To ensure there was not a systematic bias associated with the patients with missing data, outcomes were compared between these patients and those without missing data, and no differences were noted in OS (data not shown). Finally, some patients may have received their CN before the initiation of targeted therapy that may bias the OS estimate against those with CN; however, this makes the analysis more robust because it may underestimate the OS benefit.

The Clinical Trial to Assess the Importance of Nephrectomy (CARMENA; NCT00930033) will study patients with good performance status (Eastern Cooperative Oncology Group 0 or 1) and randomly assign them to nephrectomy followed by the targeted therapy sunitinib or sunitinib alone. The Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients with Metastatic Kidney Cancer (SURTIME; NCT01099423) clinical trial investigates the benefit of treating mRCC patients with sunitinib before CN as well as after, compared with sunitinib only after CN. However, these trials are not anticipated to report for some time, so these retrospective data may guide us until then. Combined, the results of these trials will have a more definitive answer for the role of CN in mRCC patients treated with targeted therapy.

5. Conclusions

Our findings demonstrate that CN may provide an OS benefit in mRCC patients treated with targeted therapy. Patients with limited expected survival or those with four or more IMDC prognostic factors may not receive a substantial benefit compared with those expected to survive longer. Stringent patient selection remains vital as we await results from the randomized controlled trials.

Author contributions: Daniel Y.C. Heng had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Heng, Choueiri.
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